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Effect of Bunaphtine on right atrial repolarisation in man

R. FENICI, M. MARCHEI, F. BELLOCCI AND P. ZECCHI

From the Cardiovascular Laboratory, Department of Medical Pathology, Catholic University of Sacred Heart, Rome, Italy

Using a bipolar suction electrode technique, right atrial monophasic action potentials were recorded in 11 patients with recurrent attacks of paroxysmal atrial tachyarrhythmia.

The right atrial monophasic action potential total duration, measured at 90 per cent level of repolarisation, in sinus rhythm, ranged between 217 and 394 ms.

N(2-diethylamine-ethyl)N(n-buthyl)-naphtamide (Bunaphtine) was administered by an intracardiac catheter at an average dosage of 1·78 mg/kg body weight in order to evaluate its effect on atrial repolarisation. Monophasic action potential recordings were performed during drug administration and thereafter every minute for an average observation period of 12·2 minutes. The drug induced a significant lengthening of atrial repolarisation (mean 18·4%) strongly correlated with a significant reduction of relative repolarisation rate of phase 3 (RRR ph3). The effect was more obvious in patients with short repolarisation and was not correlated with significant variations in heart rate. When basic cycle length was maintained constant by atrial pacing an increase in total duration of right atrial monophasic action potential was seen. Administration of the drug was followed by an appreciable reduction of inhomogeneity of repolarisation as measured from different sites in the atrium. In 2 patients conversion from atrial fibrillation to sinus rhythm occurred during drug infusion with a progressive lengthening of right atrial monophasic action potential; this suggests that the antiarrhythmic properties of Bunaphtine are related to its direct effect on repolarisation. Thus, as far as atrial tissue is concerned Bunaphtine can be considered a Class 3 antiarrhythmic drug according to the classification of Vaughan-Williams.

N (2-diethylamine-ethyl) N (n-buthyl) naphtamide (Bunaphtine)[1] is a new drug, the antiarrhythmic properties of which have been reported as being superior to those of quinidine (Beani, 1972), while circulatory side effects appear to be less; it does not significantly affect mean arterial pressure or coronary flow. In therapeutic doses it seems to be strictly cardioactive; only at toxic levels does it induce depression of the central nervous system (Beani, 1972).

Wide clinical use has proved the effectiveness of Bunaphtine in the treatment of both ventricular and supraventricular arrhythmias, either chronic or paroxysmal (Botti, 1972; Lotto and Lomanto, 1972; Masini *et al.*, 1972; Franchini *et al.*, 1974; Vegis, 1975). Good results have been obtained also in prophylactic and therapeutic use in patients with acute myocardial infarction (Botti *et al.*, 1976).

Electrophysiological properties of Bunaphtine have been studied *in vitro* on guinea-pig and rabbit heart preparations by the microelectrode technique (Ferroni and Monticelli, 1973). The primary effects of the drug on action potentials of atrial myocardial cells are a reduction or disappearance of prepotentials, a prolongation of action potential duration, a significant reduction in heart rate, and an increase in amplitude of the action potential (Ferroni and Monticelli, 1973).

Electrophysiological studies in patients, carried out by His bundle electrogram and pacing techniques, have given some information on the effects of Bunaphtine on atrioventricular conduction (Scibilia *et al.*, 1973; Grazi *et al.*, 1974), but so far little information is available about its effect on myocardial refractory periods (Grazi *et al.*, 1975).

The monophasic action potential recording technique using a suction electrode permits a good evaluation of the action potential duration and of the course of repolarisation (Hoffman *et al.*, 1959; Shabetai *et al.*, 1968; Olsson, 1971). While it cannot

[1] 1st. Farmacologico Malesci, Firenze, Italy.

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give reliable information about the depolarisation phase, it provides an exact measure of myocardial refractoriness and of rapid changes of this (Olsson, 1971). For this reason the monophasic action potential recording technique has been recommended for the accurate study of the electrophysiology of the arrhythmias and of the mechanisms of action of antiarrhythmic drugs in clinical practice (Gavrilescu and Cotoi, 1972; Olsson, 1972; Cabasson *et al.*, 1975; Fenici *et al.*, 1975). In previous observations (Fenici *et al.*, 1974a, b) Bunaphtine was found to delay repolarisation of human atrial myocardial fibres. The present study was carried out in order to evaluate the effect of Bunaphtine on right atrial monophasic action potential in patients with recurrent paroxysmal supraventricular tachyarrhythmias, in the hope of providing a more rational basis for the clinical use of the drug.

Patients and methods

Eleven patients, 6 women and 5 men, all complaining of episodes of paroxysmal atrial tachyarrhythmia, were investigated, after informed consent had been obtained, during routine electrophysiological studies or diagnostic right heart catheterisation. In all cases except one (case 1) previous cardioactive treatment, if being given, had been discontinued at least 3 days before the procedure. All the patients, except case 1, were in sinus rhythm at the beginning of the investigation. Selected clinical data from the patients are presented in Table 1.

Right atrial monophasic action potential recordings were performed using a 7F gauge bipolar electrode catheter (USCI No 5623) modified to produce a suction electrode catheter as described in more detail elsewhere (Fenici *et al.*, 1973). Absolute electrical safety of the patient was provided. Deriving a unipolar signal using a peripheral electrode, an intracardiac electrogram was obtained along with the monophasic action potential from the same recording site; this is useful for a correct evaluation of the quality of the monophasic action potential and of the level at which recording is accomplished (Olsson, 1971). For signal amplification HP 8811A bioelectrical amplifiers were used. Recordings were performed, together with continuous oscilloscopic monitoring, directly onto a magnetic tape recorder (HP 3960M), allowing easy data storage and playback in a time expanded or compressed mode, to improve data manipulation. Tracings were transferred onto photographic paper at 100 and 200 mm/s paper speed. Suction applied was mainly 350 mmHg; it was discontinued every 2 minutes to avoid the danger of irreversible myocardial lesions (Olsson, 1971). All patients tolerated the procedure without any subjective discomfort or objective complication.

After a stable monophasic action potential recording had been obtained in basal conditions, an average dose of 1·78 mg/kg body weight of Bunaphtine was delivered, directly in the right atrium, over 1 to 2 minutes. Right atrial monophasic action potential was recorded continuously from the same site during drug administration and

Table 1 *Selected data from patients*

Case No.	*Age (y)*	*Sex*	*Diagnosis*	*Electrocardiogram*	*Paroxysmal arrhythmias*	*K (mmol/l)*	*Drugs*	*Discontinued before study*
1	44	F	MS (operated); DC shock conversion of AF with frequent relapse	SR-RAO-RVO	AFl-AF	Normal	Digitalis propranolol, quinidine	3 days ND ND
2	38	F	Thyroid adenoma	SR-N	PAT	Normal	Propranolol	10 days
3	49	F	Palpitation	SR-N	PAF	Normal	None	—
4	46	F	ASD (foramen ovale); hypothyroidism, hiatus hernia	SR-N	PAT	3·2	None	—
5	66	M	Syncopal attacks; cholelithiasis	SR-AR with CSM	PAF	Normal	Atropine	3 days
6	40	F	Cholelithiasis (operated); duodenal ulcer	SR-ant. lat. ischaemia	PAT	Normal	None	—
7	25	M	Dizziness; hiatus hernia; hypertension	SR-LVH	PAF	Normal	None	—
8	50	M	Goitre (colloid-cystic adenoma-operated)	SR-PVC	PAF	Normal	Digitalis, propranolol, quinidine	3 days
9	50	F	MS; nephrovascular hypertension	SR-LAO	PAF	3·8	KCl, quinidine, amiodarone	10 days
10	71	M	Dizziness; palpitation	SR-PAC	PAF	Normal	None	—
11	60	M	Syncopal attacks; rheumatoid arthritis	SB-PAC	—	Normal	None	—

AF, atrial fibrillation; AFl, atrial flutter; AR, atrial arrest; ASD, atrial septal defect; CSM, carotid sinus massage; LAO, left atrial overload; LVH, left ventricular hypertrophy; MS, mitral stenosis; N, normal; PAC, premature atrial contraction; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PVC, premature ventricular contraction; RAO, right atrial overload; RVO, right ventricular overload; SB, sinus bradycardia; SR, sinus rhythm; ND, not discontinued.

Table 2 *Individual data from right atrial monophasic action potential recordings before and after Bunaphtine administration*

Case No.	Rhythm	Dose (mg/kg body weight	Before Bunaphtine			After Bunaphtine			RA MAP dur.		Cycle length
			RA MAP dur. (ms)	Cycle length (ms)	RRR ph3 (%/s)	RA MAP dur. (ms)	Cycle length (ms)	RRR ph3 (%/s)	Incr. (%)	VC (%)	VC (%)
1	A. Fl	0·81	137·8 ±16·24	254 ±8·22	309·12 ±39·5	257·4 ±14·89	336·2 ±4·8	157·57 ±19·21	86·79	42·8	19·7
2	SR	2	217·43 ±4·12	521 ±6·08	615·4 ±25·77	286 ±6·52	596 ±11·4	380·29 ±29·25	31·54	19	9·5
3	SR	1·3	233·6 ±4·16	764 ±23·29	384·16 ±12·4	311 ±3·08	680 ±14·26	259·15 ±9·25	33·13	20·1	8·28
4	SR	1·5	245·6 ±7·44	614·4 ±5·18	518·31 ±50·82	330·8 ±3·11	624·6 ±12·66	285·49 ±11·29	34·69	20·9	1·16
5	SR	2	261 ±7·71	577 ±2·74	478·52 ±12·81	305·2 ±10·76	592 ±2·74	417·75 ±5·06	16·98	11·04	1·81
6	SR	2	286·6 ±5·94	815·2 ±14·2	432·46 ±5·35	379 ±5·48	854 ±8·22	282·92 ±4·89	32·24	19·69	3·29
7	SR	1·6	292·7 ±13·65	754·6 ±54·77	406·1 ±17·46	317 ±4·36	812 ±7·85	300·14 ±12·63	8·3	5·64	5·18
8	SR	2·1	301 ±6·52	561 ±2·24	493·42 ±11·43	329 ±2·24	635 ±0	415·42 ±7·83	9·3	6·3	8·75
9	SR	1·8	325·72 ±27·49	994·5 ±45·35	303·01 ±43	334·29 ±16·73	1001·65 ±25·85	298·6 ±58·1	2·63	1·84	0·51
10	SR	1·5	354 ±8·54	917 ±9·70	306·6 ±19·23	374·4 ±9·96	929 ±6·52	279 ±6·93	5·76	3·96	0·92
11	(SR) AP 70/min	2	341·86 ±5·21	840	403·54 ±27·88	376·6 ±3·65	840 ±0	367·96 ±5·9	9·22	7·02	—
Mean values Cases 2-11		1·78 ±0·28	285·95 ±46·3	735·8 ±161·5	434·15 ±96·1	334·3 ±32·42	756·4 ±149·16	328·67 ±60·23	18·38 ± 13·02	11·55 ± 7·58	4·38 ± 3·64

AFl, atrial flutter; AP, atrial pacing; dur., duration; incr., increment; MAP, monophasic action potential; RA, right atrial; RRR ph3, relative repolarisation rate of phase 3; SR, sinus rhythm; VC, variation coefficient.

thereafter every minute for a mean observation time of 12·2 minutes.

In case 9 right atrial monophasic action potential recordings were obtained from 5 different sites in order to evaluate the degree of non-uniformity of atrial repolarisation before and after drug administration. In case 11 all the investigations were performed at a constant cycle length obtained by atrial pacing to eliminate the rate dependent variations in duration of right atrial monophasic action potential.

According to the criteria suggested by Olsson (1971) for quantitative analysis of the tracings, right atrial monophasic action potential total duration was measured at 90 per cent of the repolarisation and expressed in milliseconds (ms); preceding electric cycle length was also expressed in milliseconds. The relative repolarisation rate of phase 3 was expressed as a percentage of a second (%/s).

Statistical analysis was performed using the t test of paired differences and variation coefficients.

Results

Individual data from recordings before and after Bunaphtine administration are presented in Table 2.

PATIENTS IN SINUS RHYTHM

Before Bunaphtine the average right atrial monophasic action potential duration was 285·9 ±46·3 ms; the average relative repolarisation rate of phase 3 was 434·15 ±96·1 per cent/s, and the average cycle length was 735·77 ±161·9 ms. After the administration of the drug a prolongation of the average duration of right atrial monophasic action potential to 334·3 ±32·82 ms and of cycle length to 756·43 ±149·16 ms together with a reduction of relative repolarisation rate of phase 3 to 328·67 ± 60·23 per cent/s was seen (Fig. 1).

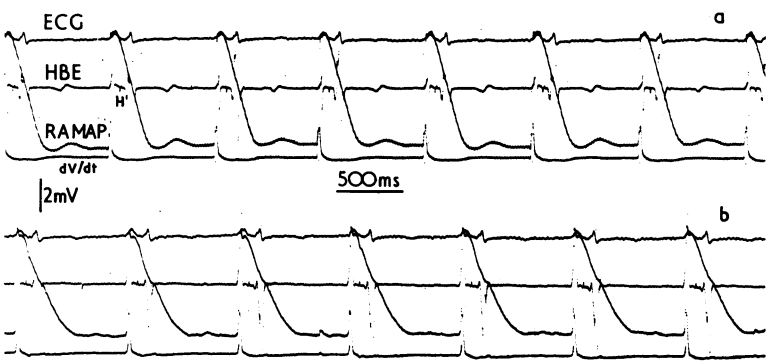

Fig. 1 *Case 6. Right atrial monophasic action potential (RA MAP) before (a) and 10 minutes after Bunaphtine (b).*

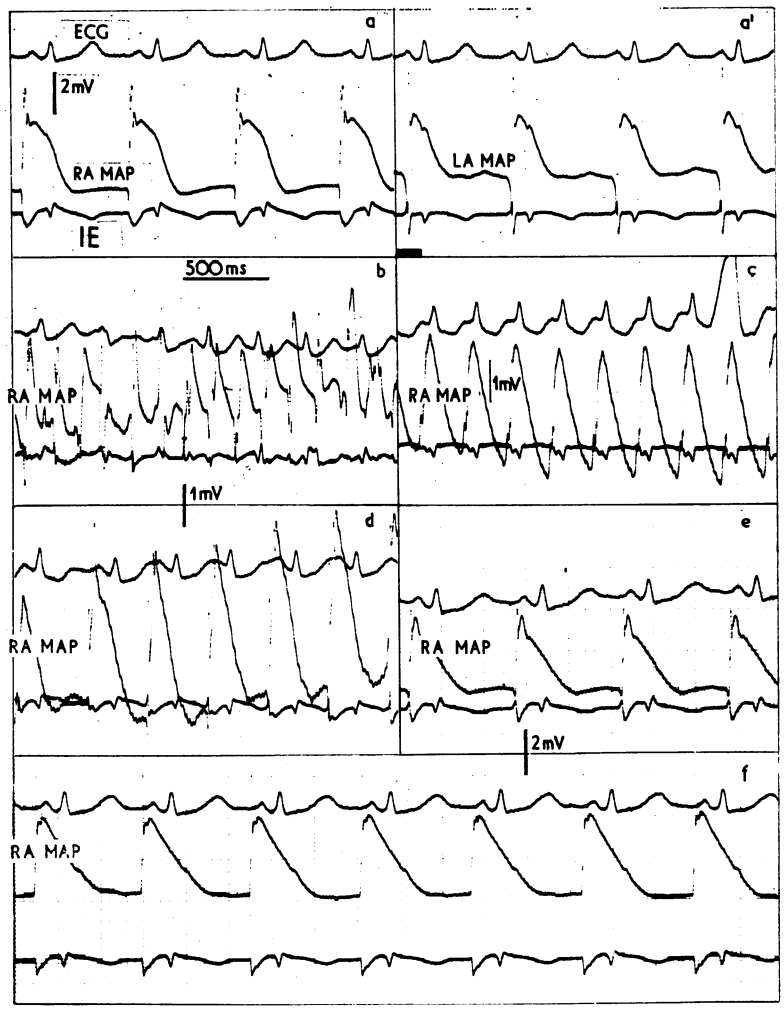

Fig. 2 *Case 4. (a-a') basic sinus rhythm (right and left atrial MAPs); (b) paroxysmal atrial fibrillation; (c) atrial flutter during drug infusion; (d) recovery of sinus rhythm (SR) (1 minute after Bunaphtine administration), (e) SR 7 minutes after Bunaphtine administration; (f) 30 minutes after Bunaphtine administration (maximum effect on RA MAP duration). IE, intracardiac electrogram.*

The average increment of right atrial monophasic action potential duration was 18·38 per cent. The average variation coefficient for monophasic action potential duration was 11·55 per cent. The largest modification of total duration of right atrial monophasic action potential was noticed at an average time of 8·1 s (range 2 to 30 s) after drug infusion.

In 2 patients (cases 4 and 10) paroxysmal atrial fibrillation occurred during the procedure and Bunaphtine was administered to regain sinus rhythm (Fig. 2 and 3). Conversion occurred in both cases with a progressive lengthening of right atrial monophasic action potential, the critical duration for the re-establishment of sinus rhythm being 195 to 210 ms. In one patient (case 4) a passage from atrial fibrillation to atrial flutter with 1:1 conduction was observed before the conversion to sinus rhythm (Fig. 2c).

In all cases a good relation between total duration of right atrial monophasic action potential and relative repolarisation rate of phase 3 variations was seen (equation for regression line $y=844{\cdot}3-1{\cdot}5x$ $r=0{\cdot}72$) (Fig. 4).

Variations of total duration of right atrial monophasic action potential and those of cycle length were poorly correlated ($y=114{\cdot}9+2{\cdot}03x$; $r=0{\cdot}61$).

Prolongation of right atrial monophasic action potential and relative repolarisation rate reduction were significant ($P<0{\cdot}0025$), while cycle length modifications were not ($P>0{\cdot}05$).

In case 9 the interindividual variation coefficient in basal conditions was 8·75 per cent; after Bunaph-

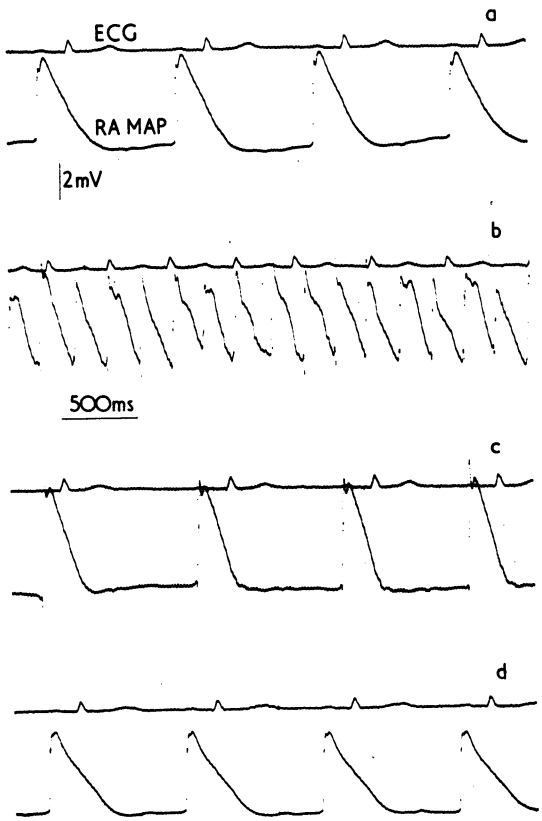

Fig. 3 *Case 10. (a) Basic sinus rhythm; (b) paroxysmal atrial fibrillation; (c) RA MAP immediately after SR re-establishment; (d) RA MAP 4 minutes after Bunaphtine administration (maximum effect on duration).*

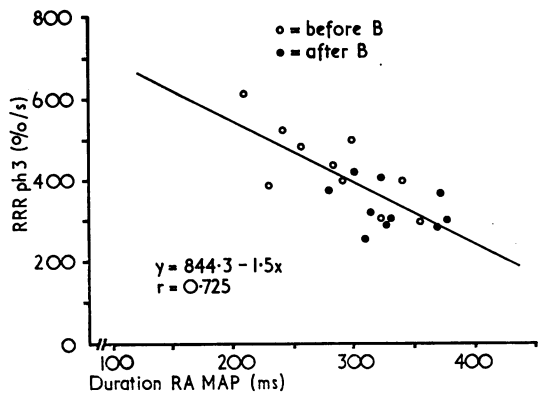

Fig. 4 *Relation between relative repolarisation rate of phase 3 (RRR ph3) and duration of right atrial MAP (RA MAP TD).*

tine administration this was reduced to 5 per cent. In this case the lowest increment in total duration of right atrial monophasic action potential was observed (2·63%). In case 11 the increment was 9·2 per cent, with a variation coefficient of 7 per cent; the interindividual variation coefficient before drug administration was 4·19 per cent.

PATIENT IN ATRIAL FLUTTER (FIG. 5)

(This case was not included in the statistical evaluation because previous cardioactive treatment had not been withdrawn and could have distorted the results.)

Basal right atrial monophasic action potential total duration was 137·8 ms; after Bunaphtine prolongation up to 257·4 ms was observed without

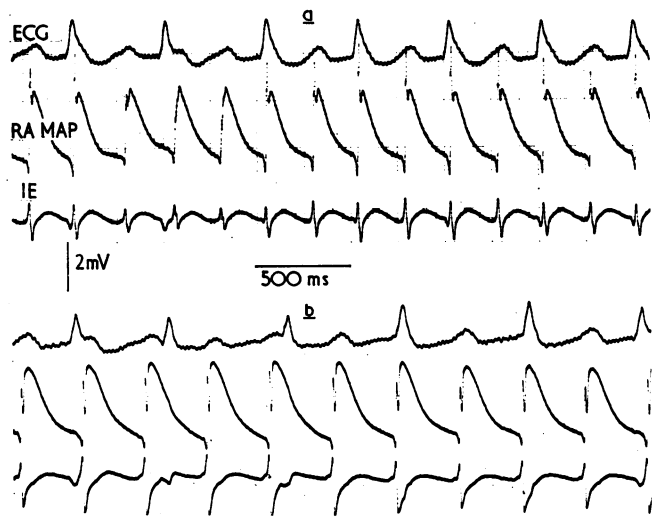

Fig. 5 *Case 1. Persistence of atrial flutter in spite of significant RA MAP prolongation after Bunaphtine (b). IE, intracardiac electrogram.*

conversion to sinus rhythm. The increment of right atrial monophasic action potential total duration was 86·79 per cent and was strongly related to a significant prolongation of cycle length ($y=210·1+1·37x$; $r=0·99$).

Discussion

A short monophasic action potential duration has been shown to be present in a number of patients with paroxysmal supraventricular arrhythmias (Olsson, 1972; Olsson *et al.*, 1973). In our study only 4 of the 10 patients in sinus rhythm had a rather short right atrial monophasic action potential; the shortest monophasic action potential was found in a patient with a clinical picture of hyperthyroidism in accord with *in vitro* observations (Freedberg *et al.*, 1970; Johnson *et al.*, 1973).

Bunaphtine administration induced a significant prolongation of right atrial monophasic action potential (average 18·38%). As can be seen from Table 2 the largest increment was in patients with a short basic repolarisation (average 29%), while a smaller effect (average 7·1%) resulted when basic right atrial monophasic action potential duration was within normal range. Prolongation of the right atrial monophasic action potential can in part be explained by a significant reduction in heart rate if it occurs (Olsson, 1971); in our study, however, only a slight increase in cycle length was found which was not statistically significant. A clear-cut correlation between right atrial monophasic action potential prolongation and heart rate reduction was evident only in case 1. When the heart rate was maintained constant by atrial pacing (case 11), an increase in total duration of right atrial monophasic action potential (7%) was still seen. This implies that Bunaphtine induces to a certain extent a prolongation of right atrial monophasic action potential as a direct effect. A reduction of relative repolarisation rate of phase 3, strongly correlated to prolongation of right atrial monophasic action potential, was seen after drug infusion in all cases.

The processes governing the shape and duration of repolarisation of cardiac action potential are complex and controversial and have recently been described in a mathematical model (McAllister *et al.*, 1975).

As acetylcholine enhances K^+ permeability in the atrial myocardium (Hoffman and Cranefield, 1960), and vagal stimulation induces a reduction in duration of right atrial monophasic action potential (Samuelsson, 1973) so that the effect of Bunaphtine could be explained as an indirect action on atrial repolarisation by a vagolytic effect; but pharmacological studies contradict this hypothesis (Beani, 1972; Sanna *et al.*, 1974).

The prolongation of repolarisation was most consistent when the basic refractory period was short. In addition to prolonging the duration of atrial repolarisation Bunaphtine also reduced the degree of variation in this duration as recorded from different sites in the same atrium. This normalisation of refractoriness may result in the blocking of re-entry pathways in the atrium leading to an antiarrhythmic effect as a result of the reduction of inhomogeneity of repolarisation. In the 2 patients who developed paroxysmal atrial fibrillation during the procedure (cases 4 and 10), conversion to sinus rhythm was seen during drug infusion, when the duration of right atrial monophasic action potential reached about 200 ms; this value is critical for the re-establishment of sinus rhythm (Gavrilescu and Cotoi, 1972; Olsson, 1972). Immediately after recovery of sinus rhythm the right atrial monophasic action potential duration was still short (Fig. 2d to 3c), and there was a tendency to repetitive arrhythmias. After the final drug-induced normalisation of monophasic action potential duration, full stability of rhythm was achieved (Fig. 2f to 3d). Persistence of atrial flutter in case 1, in spite of the significant prolongation of right atrial monophasic action potential (Fig. 5b), is not clear and seems to contradict the observations in the other 2 patients. It could be related to the lower dose employed, which was sufficient to reduce heart rate. Monophasic action potential prolongation, therefore, could be explained as a rate-dependent modification. Moreover in this patient the effect of other cardioactive drugs was already present.

As stated by Olsson (1971, 1974) the expected variability in a single subject of the atrial monophasic action potential duration between successive applications of the suction electrode can be expressed as a variation coefficient ranging from 0 up to 16·5 per cent. In our patients, with at least 5 applications of the electrode at different sites of the right atrium, an intraindividual variation coefficient ranging from 3·3 to 8·75 per cent was found; this was considered to be an expression of the range of variability of repolarisation duration in the basal condition.

An increased variability or inhomogeneity of the repolarisation of the myocardial fibres may allow development of a re-entry mechanism which could lead to arrhythmias (Sarachek *et al.*, 1972; Wit *et al.*, 1974). In case 9 right atrial monophasic action potential duration was well within normal limits but a wide intraindividual variation coefficient was found (VC=8·75%), which could account for the clinical picture. After Bunaphtine, the intraindividual variation coefficient was lessened

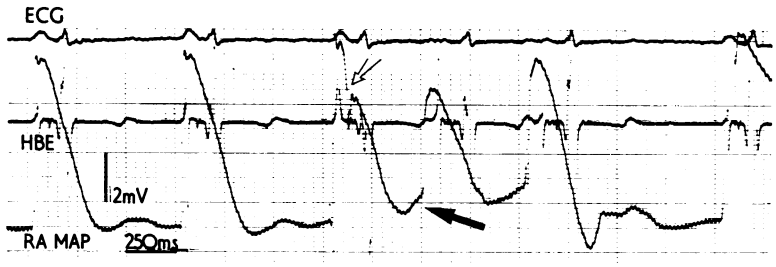

Fig. 6 *Evidence of phase 4 depolarisation (black arrow) during a run of premature atrial contractions. (An atrial fusion beat is also appreciable: white arrow.)*

(VC=5%), suggesting a reduced dispersion of repolarisation; this suggests that an alternative action of the drug is to improve the spread of the excitatory wave-front. To test this hypothesis would require further investigations with a more appropriate technique, such as proposed by Sarachek *et al.* (1972).

Variation coefficients between monophasic action potential durations before and after Bunaphtine were also calculated in individual patients and were employed as an index of the significance of the drug's effect. A higher variation coefficient was found in patients with a shorter duration of right atrial monophasic action potential (average 17·85%), while a lower one was observed in those with a normal repolarisation (average 4·95%).

A slow phase 4 depolarisation, suggestive of latent pacemaker activity (Hoffman and Cranefield, 1960), was found in 3 patients; it was much more evident during a run of premature atrial beats (Fig. 6). After Bunaphtine administration a reduction of prepotential was apparent from inspection of the tracings, but, because of technical limitations, no quantitative evaluation was possible.

The classification of antiarrhythmic drugs is still controversial. Most authors favour an electrophysiological approach (Mason *et al.*, 1973; Sanna *et al.*, 1974; Singh and Hauswirth, 1974; Vaughan Williams, 1975). Monophasic action potential recording alone does not allow an exhaustive evaluation of all properties of an antiarrhythmic drug. It provides information about the local action potential duration, repolarisation uniformity, and instantaneous modifications of cellular refractoriness. Using a pacing technique, an evaluation of the effects of the drug on the effective refractory period/monophasic action potential duration ratio could also be accomplished. Bunaphtine should increase this ratio (Sanna *et al.*, 1974).

In previous electrophysiological clinical studies a depressive effect of Bunaphtine on intra-atrial conduction velocity has been shown (Scibilia *et al.*, 1973; Grazi *et al.*, 1974). The present work appears to confirm, in the human beating heart, what has been observed in *in vitro* investigations (Ferroni *et al.*, 1973), regarding the Bunaphtine-induced prolongation of atrial action potentials. As far as atrial tissue is concerned, therefore, Bunaphtine is a class 3 antiarrhythmic drug according to the classification of Vaughan-Williams (Vaughan Williams, 1975).

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Requests for reprints to Dr. R. Fenici, Servizio di Cardiologia, Universita Cattolica del S. Cuore, Roma, Largo Gemelli 8, Italy.